Goodpasture’s disease

A. N. Turner

Renal Medicine, University of Edinburgh, UK

Introduction

Goodpasture’s disease (also known as Goodpasture syndrome, anti-glomerular basement membrane disease, anti-GBM disease) is an uncommon yet well-known condition because of the striking way in which it can cause rapid destruction of the kidneys and bleeding into the lungs. A patient with this syndrome was first described by Ernest Goodpasture in 1919. However, it is now known that several diseases can cause a similar presentation. Goodpasture’s name is most usefully reserved for those with anti-GBM disease.

Pulmonary–renal syndrome

Most pulmonary–renal syndromes involve neither nephritis nor lung haemorrhage. The commonest cause is fluid overload and pulmonary oedema in a patient with acute or chronic renal failure of any cause. Pulmonary haemorrhage and nephritic renal disease imply a much more restricted range of possibilities, of which the most frequent is small vessel vasculitis (usually Wegener’s or microscopic polyangiitis). However other diseases may cause diagnostic uncertainty [1].

Goodpasture’s disease

The typical patient [1] has both lung and kidney disease. However the disease may also cause lung disease alone, or kidney disease alone. It is rare: approximately 0.5–1 case per million people per year has been estimated in European populations, and it is rarer than in Black and Asian races. While it has occurred in patients as young as 4 and as old as 80 years, it is most common at ages 18–30 and 50–65. Men and women are almost equally affected.

Kidney disease

Glomerulonephritis is usually only recognized when an explosive acceleration of the disease process occurs, so that renal function can be lost in days (rapidly progressive glomerulonephritis, RPGN). If there is isolated renal disease there may be symptoms only of renal failure, and the presentation is often late.

Lung disease

Commonly the first lung symptoms develop days, weeks, or months before kidney damage becomes evident. At its most severe, lung haemorrhage may cause severe impairment of oxygenation so that intensive care and artificial ventilation are needed. However, at the other extreme it may only cause dry cough and minor breathlessness. In occasional patients relatively mild symptoms may go back over many years. Presentation with ‘isolated’ lung disease (in fact there is usually at least haematuria) is not uncommon overall, although it is uncommon enough in any physician’s lifetime for it to lead to the publication of one or two case reports on the topic every year.

Sometimes patients are anaemic because of bleeding episodes into the lungs over many weeks or months. In Goodpasture’s disease, lung haemorrhage mostly occurs in current cigarette smokers or those with damage caused by infection, fluid accumulation, or exposure to fumes such as paint or gasoline. This is not true of most of the other conditions that can cause lung haemorrhage and RPGN. Haemoptysis may be a poor guide to how severe the lung disease is, but as with the kidney disease, and often at the same time, deterioration may occur very rapidly. It is often only at this stage that the patient seeks medical attention.

Diagnosis

Because the early symptoms are characteristically vague, and because of the tendency of the disease to undergo very rapid progression, it is common for the
true diagnosis to be reached at a late stage. Tests for anti-GBM antibodies in the blood can be very useful, but many assays are available and false positive and false negative results are found with some of these. Testing for anti-GBM antibodies should always be combined with tests for ANCA (antibodies to neutrophil cytoplasmic antigens), as the clinical presentation of small vessel vasculitis may be very similar, and the two types of autoantibody can occur together. Despite the availability of serological tests, renal biopsy is almost always necessary. It is often the quickest way to secure a diagnosis, and even if the diagnosis looks certain, it gives valuable prognostic information.

Treatment

Effective combination treatment was developed in the 1970s, the first effective treatment for an aggressive nephritis. The major elements of the treatment today are very similar. Lung haemorrhage is usually arrested in days, and further renal damage can be prevented.

- Prednisolone—1 mg/kg orally once daily, reducing progressively.
- Cyclophosphamide—2 mg/kg orally once daily rounded down to the nearest 50 mg, and in reduced dose for patients over 60 years.
- Plasma exchange—introduced to remove anti-GBM antibodies, as they appear to be responsible for at least some of the tissue damage. It appears to be particularly effective if there is lung haemorrhage or very acute renal disease.

Toxicity

The most important risk of treatment is serious infection. All three components contribute to this. Furthermore, infection may accelerate the disease process. All three arms of the treatment also carry additional risks of their own. Because of these risks, some patients may be best left untreated. These are those with severe and irreversible renal damage in the absence of any signs of lung haemorrhage. This decision has to be taken carefully after the diagnosis is secure and kept under review.

Duration

Three months of full treatment is usually enough to suppress anti-GBM antibody production, after which cyclophosphamide can be stopped and prednisolone tailed off. Relapses after this time are uncommon if a full course of treatment has been given. In some instances they appear to be related to resuming cigarette smoking. Without treatment, anti-GBM antibodies may remain in the blood for a year or more before disappearing. Patients who have ANCA as well as anti-GBM antibodies are generally given treatment for longer than 3 months.

Information

Our increasingly well-informed patients must nowadays be made aware of the risks of treatment, but also that the risks of the untreated disease are substantial. Information for the layman is difficult to find: we have published some patient-orientated information on the Internet [2].

Outcome

Twenty-five years ago Goodpasture’s disease was usually fatal. Death from lung haemorrhage may still occur before the diagnosis has been made, or in the first few days of treatment before it has been controlled. Lung haemorrhage may also be reactivated by infection, fluid overload, or lung toxicity (e.g. caused by cigarette smoking). Acute renal failure also remains a severe illness with a significant mortality, particularly if the patient is old or suffering from other diseases. Immunosuppressive treatment puts the patient at increased risk of a variety of common and uncommon infections, from infected intravenous lines to pneumocystis pneumonia, and these are the commonest causes of death after the first week. This is minimized by the short duration of treatment in this disease, but immunosuppression is intense in the early part of therapy.

With treatment, lung disease usually recovers completely. Unfortunately kidneys are less able to repair themselves, and those with severe renal involvement are often left with permanent renal failure and face a life of renal replacement therapy.

Renal transplantation

Transplantation can be safely carried out in Goodpasture’s disease after anti-GBM antibodies are no longer detectable. It is sensible to leave an interval of at least 6 months after the first negative result (this will depend on the sensitivity of the test being used). This may be a problem if no treatment was given at the outset, as the time for safe transplantation may then be 2 years or more away. These precautions have largely removed the problem of destruction of transplants caused by return of Goodpasture’s disease.

Sometimes ‘de novo’ anti-GBM disease is identified after renal transplantation. Almost always this occurs in patients with Alport syndrome (recognized or unrecognized) who have developed an immune response to antigens present in the transplanted organ that they themselves lacked [3].
What causes Goodpasture’s disease?

For most autoimmune conditions it is hypothesized that disease initiation occurs in response to some sort of environmental trigger in predisposed individuals. There is evidence for both of these in Goodpasture’s disease.

The association of Goodpasture’s disease with specific HLA types is very strong [4]. Both positive (HLA-DR15) and negative (HLA-DR7) associations are observed. This is being utilized to develop understanding of antigen presentation, tolerance, and autoimmunity in Goodpasture’s disease.

There are also clues to the nature of environmental or acquired risk factors [5]. Very occasionally the disease has developed after lithotripsy or some other kinds of kidney trauma. Membranous nephropathy, in which the GBM is expanded by an increased amount of Goodpasture antigen-containing basement membrane material, is rarely associated with crescentic deterioration involving anti-GBM antibody formation. More commonly, inhaling noxious substances such as cigarette smoke causes lung haemorrhage—but most of the people to whom this occurs probably had the disease already (Table 1).

Conclusion

Goodpasture’s disease is an important disease in its own right, but has an even more significant role as a ‘model’ of autoimmune kidney damage, both in animals and in man. Treatments designed for this disease have been widely applied in nephrology and elsewhere—often with greater effect. It is likely to be the source of further understanding in the future.

| Table 1. Milestones in Goodpasture research (abbreviated from [2]) |
|------------------------|----------------------------------|
| 1900–1950s            | Antibodies can cause kidney damage in animals |
| 1960s                 | Antibodies cause kidney damage in man |
| 1970s                 | Effective treatments are developed |
| 1980s                 | Lung haemorrhage only occurs if the lungs are damaged |
| 1990s                 | Infection increases damage caused by immune attack |
| 2000s                 | Antibodies bind to a single component of GBM |
| 2010s                 | The Goodpasture antigen is missing from GBM in Alport syndrome |
| 2020s                 | Some people are genetically at risk of Goodpasture’s disease |
| 2030s                 | The Goodpasture antigen is a new type IV collagen chain |
| 2040s                 | Alport syndrome usually caused by COL4A5 mutations |
| 2050s                 | The Goodpasture antigen and its gene (COL4A3) are identified |
| 2060s                 | Understanding of Alport anti-GBM disease |
| 2070s                 | Peptides presented to T cells identified |

References